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Relationship of Sleep Abnormalities to Patient Genotypes in Prader-Willi Syndrome

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To assess whether sleep abnormalities are related to the genetic abnormalities in Prader-Willi Syndrome (PWS), we performed polysomnographic studies (nighttime and daytime) and determined the chromosome 15 genotypes in eight patients with PWS. Four patients demonstrated sleep onset REM periods (SOREM), and five met the objective polysomnographic criteria for severe or moderate excessive daytime sleepiness (EDS). Three of the four patients with SOREM displayed a paternally derived deletion of chromosome 15q11-q13, whereas the fourth exhibited maternal uniparental heterodisomy in this chromosomal region (UPD). Two of the four patients that did not display SOREM carried paternally derived deletions; the remaining two demonstrated UPD. Four of the five patients with EDS displayed paternal deletions, and the fifth exhibited UPD. One of three patients without evidence of EDS demonstrated paternal deletion; the remaining two showed UPD. Although neither EDS nor SOREM was not consistently associated with a specific genetic abnormality, these phenotypes may be more common in patients with paternal deletions than in those with UPD. Sleep abnormalities in PWS cannot be explained by a single genetic model. © 1996 Wiley-Liss, Inc.

KEY WORDS: Prader-Willi, EDS, SOREM, deletion, heterodisomy

INTRODUCTION

Prader-Willi syndrome (PWS) is a congenital condition characterized by neonatal hypotonia, hypogonadism, obesity, behavior problems (associated with hyperphagia), mild mental retardation, and short stature [Greenswag and Alexander, 1988; Butler, 1989; Holm et al., 1993]. Excessive daytime sleepiness (EDS) and REM abnormalities are more prevalent in older children and adults with than in the general population. Their frequency in PWS subjects varies from 30% to ~70% [Vela-Bueno et al., 1984; Helbing, 1993; Hertz et al., 1993; Clift, 1994]. Although there is some disagreement over the frequency of sleep apnea in PWS patients [Vela-Bueno et al., 1984; Harris and Alley, 1985; Helbing et al., 1993; Hertz et al., 1993; Kaplan et al., 1991; Clift et al., 1994; Friedman et al., 1984], most investigators agree that the REM abnormalities and EDS appear to be independent of respiratory disturbances or even of obesity [Vela-Bueno et al., 1984; Helbing et al., 1993; Hertz et al., 1993a; Kaplan et al., 1991; Clift et al., 1994; Vgontzas et al., 1995]. These findings indicate that the sleep abnormalities in PWS are apparently a component of the PWS phenotype.

PWS develops from a failure to express paternally derived genes in the q11-q13 domain of chromosome 15 [Nicholls, 1993]. Uniparental inheritance of genes whose expression is dictated by parental origin has been termed aberrant genomic imprinting. Deletions in the paternally derived chromosome 15 occur in 70% of PWS patients. The majority of the remaining individuals inherit two maternally derived chromosomes 15, termed uniparental disomy (UPD) [Mascari et al., 1992]. Patients with deletions tend to be more hypopigmented when compared to their first-degree relatives than those with UPD [Ramsey, 1992]. This suggests that not all of the phenotypes seen in PWS patients result from abnormal imprinting of genes in the Prader-Willi critical region.

It has been proposed that REM abnormalities, but not breathing abnormalities, are more frequent in PWS patients with evidence of a cytogenetic deletion of chromosome 15q [Hertz et al., 1993b]. Unfortunately, karyotypic analysis fails to detect nearly 50% of PWS patients with paternally derived deletions [Robinson et al., 1991]. This approach, together with the failure to consider maternal UPD, did not permit establishment of potential relationships between the sleep abnormalities and the diagnosis of PWS. In this study, we

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attempted to relate the genetic etiology of PWS to these sleep abnormalities.

MATERIALS AND METHODS

Subjects

Eight subjects (seven females, one male) ranging from 6 to 40 years of age participated in our study (Table I). Two of them were referred by a Prader-Willi home for evaluation of EDS. The other six were recruited randomly from a list of eight PWS patients (two patients refused to participate) who had been previously diagnosed with molecular techniques by the Division of Genetics, Department of Pediatrics (PKR and MM) and lived close to our sleep laboratory facility. Patients were selected based on their geographic proximity (no more than 2 hours from our facility) and their willingness to participate in the study. None of the subjects were being treated with growth hormone, ketogenic diet, or stimulant medication. Only one subject was being medicated with an antidepressant that was discontinued 2 weeks prior to the time of the polysomnographic studies.

Sleep Lab Procedures

All of the patients were evaluated in the sleep laboratory for one night in accordance with standard methods [Rechtschaffen and Kales, 1968]. In addition, following nocturnal polysomnography, the patients were recorded for two (1-hour each) daytime naps (9:00–10:00 a.m. the first nap and 12:30–1:30 p.m. the second nap) as previously described [Kales et al., 1987]. The sleep records were scored, independent of any knowledge of the experimental conditions, according to standardized criteria [Rechtschaffen and Kales, 1968].

Respiration was monitored throughout the night by thermocouples at the nose and mouth (model TCT 1R, Grass Instrument Co.) and by thoracic strain gauges. All-night recordings of hemoglobin oxygen saturation were obtained using an oximeter (Pulse Ox, Nonin, Plymouth, MN) attached to an earlobe.

Sleep onset and REM latency were determined for each recording in the following manner: the onset of sleep was established by the presence of any sleep stage for a duration of 1 minute or longer. However, if the initial stage of sleep was Stage 1, it had to be followed, without any intervening wakefulness, by at least 60 seconds of Stages 2, 3, 4, or REM. Sleep latency was defined as the time elapsed from lights out to sleep onset. A sleep latency of 5 minutes or less was considered as objective evidence of severe EDS, while a sleep latency of >5 minutes, but <10 minutes, was evidence of moderate EDS [Richardson et al., 1978; Kales et al., 1987]. REM latency was defined as the total amount of time from sleep onset to the first appearance of REM sleep. Finally, SOREM was determined as the occurrence of REM sleep within the first 10 minutes following sleep onset [Mitler et al., 1979].

Apnea was considered present if breathing ceased for 10 seconds or more. Hypopnea was defined as at least a 50% decrease in thermocouple output with associated oxygen desaturation of at least 4%. Oxygen desaturation was evaluated in terms of minimum oxygen saturation during wakefulness, NREM sleep, and REM sleep.

Cytogenetic and Molecular Studies

Chromosal and molecular studies to identify paternally derived deletions or maternal UPD were carried out for each patient using previously described techniques [Mascari et al., 1992; Woodage et al., 1994]. The following polymorphic genetic markers were used in the present study: D15S541, D15S11, D15S128, D15S97, GABRB3, D15S165, D15S118, CYP19, D15S117, D15S125, D15S110, D15S95, D15S111, D15S100, D15S107, D15S642. Sequences of oligonucleotide primers and conditions for polymerase chain reaction amplification were obtained from the Genome Database (NCBI, National Library of Medicine, Bethesda, MD).

Diagnostic DNA methylation studies of patient genomic DNA were performed in those instances where only one parent was available for study. Probe PW71B (D15S63) was used to detect differences in DNA methylation of the paternally and maternally derived chromosomes 15 [Dittrich et al., 1992; Buiting et al., 1994].

Data Analysis

Assessment of EDS, sleep onset REM (SOREM), and sleep organization was blinded with respect to the molecular genetic diagnostic studies. The results of the two studies were then compared to determine whether any of the sleep abnormalities present were associated with a particular genotype or mode of inheritance.

RESULTS

Molecular Genetic Studies

Deletion. Molecular deletions at genetic loci D15S10, D15S12, and D15S9 have been described in patients PW2 and PW8 [Mascari et al., 1992]. PW16 was also shown to carry a deletion of paternal alleles at D15S9, D15S11, D15S12, and D15S10 [Mascari, 1991].

In the present study, PW31 demonstrates a paternally derived deletion at D15S12 and D15S9. Since the mother of patient PW32 was unavailable, the diagnosis was based on the inheritance of non-paternal alleles only at these genetic loci and the results of DNA methylation studies at D15S63. Patient PW32 displays complete methylation at D15S63, consistent with that seen in other PWS patients. Furthermore, paternal alleles were not evident at the 15q11-q13 genetic markers, D15S541, D15S11, and D15S128. Both paternal and non-paternal alleles are present for genetic markers outside of the PWS common deletion interval, including D15S165, D15S118, CYP19, D15S95, D15S100, D15S107, and D15S87. These results suggest that PW32 harbors a paternally derived deletion of chromosome 15q11-q13.

Uniparental disomy. PW25 and PW27 have been shown previously to exhibit maternal UPD for chromosome 15 [Mascari et al., 1992]. Both of these patients had been shown to be heterozygous for one common parental allele and informative for a maternally derived allele. In the present study, maternal heterodisomy has been confirmed in the PWS critical genetic region at D15S11 in both patients.

TABLE I. Clinical Sleep and Genetic Profiles of PWS Subjects

Patient	PW2	PW8	PW16	PW25	PW27	PW31	PW32	PW33
Age (yrs)	6	25	12	22	24	19	21	40
Sex	F	F	F	F	F	F	F	M
Height (cm)	103	141	119	146	146	150	141	151
(%)[a]	<5	<5	<5	<5	<5	<5	<5	<5
Weight (kg)	24.09	87.73	38.18	69.09	65.45	78.18	53.64	52.27
(%)[a]	78	95	21	78	72	91	31	5
SOREM[b]	–	–	+	–	+	+	+	–
EDS[c]	None	Severe	Moderate	None	Moderate	Severe	Severe	None
Genotype (15q-11q13)	Paternal deletion	Paternal deletion	Paternal deletion	Maternal heterodisomy	Maternal heterodisomy	Paternal deletion	Paternal deletion	Maternal heterodisomy
Genetic studies	A, B[d]	A, B[d]	A, B[d]	A, B[d]	A, B[d]	B,C[d]	B, C[d]	A, B, C[d]

[a] Indicates percentiles of anthropometric measurements of PWS compared to normative data controlled for age and sex [U.S. Dept. HEW, 1977; Butler and Meaney, 1987].
[b] Defined by a REM latency ≤10 minutes.
[c] Defined by a sleep latency of ≤5 minutes (severe) or ≤10 minutes (moderate).
[d] A = cytogenetic analysis; B = polymorphic genetic markers; C = methylation-sensitive restriction digestion/Southern hybridization.

Since the father of patient PW33 was not available, the diagnosis was made on the basis of DNA methylation studies and the likelihood of detecting exclusive maternal inheritance for those genetic markers studied. The maternal and proband genotypes of eight highly polymorphic, genetic markers located throughout chromosome 15 were identical. For loci where his genotype is homozygous for a single allele, PW33 either harbors a paternally derived deletion at some of these loci, maternal isodisomy, or he has inherited the same allele from each parent at all of these loci. It is unlikely, that the maternal and paternal genotypes share at least one common allele and that paternal allele was transmitted at four of these loci (D15S11, D15S122, D15S541, GABRB3; $p = 0.00025$). The identical maternal and proband genotypes probably indicate the absence of paternally derived alleles due to maternal UPD. PW33 displays reduction to homozygosity for heterozygous maternal markers at all loci telomeric to D15S95, consistent with heterodisomy proximal to and isodisomy distal to this locus.

Sleep Studies

Daytime sleepiness and SOREM abnormalities. Five of the eight patients demonstrated either severe (N = 3) daytime sleepiness (SL ≤ 5 minutes in at least one of these naps) or moderate (N = 2) daytime sleepiness (SL ≤ 10 minutes but > 5 minutes).

Four of the eight patients presented SOREM during at least one of the naps, whereas two of them demonstrated SOREM during both naps (Table I). Two additional subjects presented REM sleep in the second nap. No significant weight effects were detected for SOREM or objective EDS.

Subjective data as reported by family members or caretakers indicated some degree of sleepiness in all except one of these patients. Seven take voluntary naps regularly (four of them both in the morning and afternoon, two only in the afternoon, and one only in the morning), and EDS was reported in six of these patients. Five of these six subjects met the objective criteria for severe or moderate EDS.

Respiration. None of the eight patients showed any polygraphic evidence of obstructive or central sleep apnea. Two patients demonstrated 10 and 8 apneic/hypopneic events, respectively throughout the 8-hour recording. None of the patients showed significant hypoven- tilation. S_aO_2 during NREM and REM sleep dropped below 90% in two patients for brief periods. The presence of this mild hypoventilation did not affect the quality of nocturnal sleep, i.e., the frequency of arousals. Also, there was no clear relationship between minimum S_aO_2 and presence of EDS or SOREM during daytime napping.

Nighttime sleep. No evidence of sleep disturbance in terms of prolonged wakefulness or multiple arousals was noted during nighttime sleep. Detailed nocturnal sleep data are presented elsewhere [Vgontzas et al., in press].

Relationship of EDS and SOREM to Molecular Genetic Abnormalities

There was no consistent genetic abnormality seen in patients with EDS or SOREM (Table I). Four of the

five subjects with EDS displayed a paternal deletion, whereas a fifth showed uniparental maternal heterodisomy in 15q11-q13. Three of the subjects with SOREM displayed a paternal deletion; the fourth showed maternal heterodisomy. These findings suggest that if these phenotypes have a genetic basis, EDS and SOREM do not appear to be due to haploinsufficiency for one or more genes that reside in this genetic interval.

Four patients with PWS did not display REM onset sleep abnormalities. This group contained two patients with paternally derived deletions and two with maternal uniparental heterodisomy. With respect to genotype, they are indistinguishable from those with SOREM.

DISCUSSION

Sleep Abnormalities in PWS Are Not a Direct Consequence of Genetic Abnormalities

EDS and SOREM were not exclusively associated with any particular chromosome 15q11-q13 genotype. Assuming that sleep abnormalities are fully penetrant in PWS, the finding of patients with UPD or deletions demonstrating normal sleep patterns suggests that these phenotypes are not related to the failure to express imprinted gene(s) in the PWS critical genetic interval. Since patients with maternal UPD and with paternal deletions both exhibit sleep abnormalities, the number of copies of expressed, non-imprinted genes in this genetic interval also appears to be unrelated to the etiology of the sleep disorder.

Another possibility is that EDS or SOREM is caused by a common recessive mutation in a gene that resides in the critical genetic interval for PWS. In studies of other recessive disorders [Cavenee et al., 1983; Zhu et al., 1992], patients carrying deletions are more likely to unmask and express a mutant allele than those with either normal inheritance or UPD. The possibility that these sleep abnormalities are due to mutations in a recessive locus on 15q is supported by evidence that four of the five patients with deletions displayed either EDS or SOREM or both phenotypes. However, the case of PWS27 is at odds with a recessive mode of inheritance for EDS or SOREM. This patient also presents with these sleep abnormalities and exhibits maternal heterodisomy in this genetic interval. The patient's and her mother's genotypes are identical in this region; however, her mother has no documented history of either EDS or SOREM. Either incomplete penetrance of this phenotype in the patient's mother or a second mutation in PWS27 inactivating both alleles could account for these disparate phenotypes.

Dominant inheritance of EDS and SOREM in PWS would be unlikely, since the incidence of these abnormalities in patients with PWS should then be comparable to its frequency in the general population. In fact, PWS patients exhibit these abnormalities at a significantly higher frequency (50–60%) than normal controls (5%) [Kales et al., 1987].

EDS and SOREM were more common among the patients with paternally derived deletions of chromosomes than in those with maternal UPD. These results are consistent with the increased prevalence of sleep abnormalities that has been observed in patients with detectable cytogenetic 15q11-q13 deletions [Hertz et al., 1993b]. To confirm that EDS and SOREM are more prevalent in PWS patients carrying deletions, studies with a larger number of subjects are needed.

EDS and SOREM Are Frequent in PWS and Independent of Breathing Abnormalities

Four of eight patients (or three of the *six randomly* selected subjects); 50% in either case) showed SOREM in one or both naps. This percentage is similar to that reported in previous studies [Vela-Bueno et al., 1984; Helbing et al., 1993]. The lower figure reported by Hertz et al. [1993] (2/15) might be explained by the higher BMI and the presence of hypoventilation in the majority of patients in their study. It has been shown that hypoxemia and obesity decrease REM sleep and extend REM latency [Laszy and Sarkali, 1990; Vgontzas et al., 1994], thus possibly masking underlying REM abnormalities.

Nearly all of our patients were reported subjectively to experience some form of daytime sleepiness. Five showed objective signs of daytime sleepiness. However, only one of the six randomly selected patients showed severe EDS (SL $\leq$ 5 minutes). Severe EDS occurred less frequently in the present study than in previous reports showing 8 of 14 patients [Clift et al., 1994] and 6 of 15 patients [Hertz et al., 1993] with these symptoms. The higher prevalence of severe EDS in these studies might be due to the significant proportion of subjects who were morbidly obese (BMI $>$ 39) and who displayed sleep apnea or hypoxemia.

Our finding that sleep apnea is uncommon in patients with this disorder is consistent with other studies that report respiratory data [Vela-Bueno et al., 1984; Helbing et al., 1993; Hertz et al., 1993; Kaplan et al., 1991; Vgontzas et al., 1995]. The present results further support the view that EDS and SOREM are independent of breathing abnormalities. However, breathing abnormalities and obesity may have additive effects on daytime sleepiness in patients with PWS [Hertz et al., 1993; Clift et al., 1994].

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